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April 5, 2002

Susan D. Brienza
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Ms. Gloria Chang
Center for Food Safety and Applied Nutrition
Project No. 79418
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: Information requested to Supplement NDI Notification for Iron Aid™, on behalf of Chemi Nutraceuticals, Inc.

Dear Ms. Chang:

This letter is in response to your telephone calls to our office of March 25, 2002 and March 28, 2002 concerning additional information requested for the NDI Notification we recently filed concerning the new dietary ingredient IronAid™. At the outset, I want to state very straightforwardly and clearly--as we did in the original Notification--that Chemi does not manufacture finished product, that is, a dietary supplement containing IronAid™. Instead, Chemi manufactures IronAid™ as a bulk ingredient, and will sell this ingredient to dietary supplement manufacturers. That is why we have included in the Notification—in several places—that we recommend certain label language to purchasers of IronAid™ and that if such manufacturers use a form or amount of IronAid™ different from those described in the Notification, then they must file their own NDI Notification.

On behalf of Chemi Nutracueticals, Inc. ("Chemi"), and after consulting with my client, I am supplying the answers to the specific questions you raised, here in this cover letter. In addition, this information below has also been incorporated within the revised NDI Notification attached.

[1] In what form will IronAid™ be marketed? For example, will it be in powder, crystal, or liquid extract form?

IronAid™ is a raw material (ingredient), which will be marketed to the nutritional products industry, for use in dietary supplements. IronAid™ is a reddish-brown colored, free-flowing powder.

[2] Does IronAid™ contain any "other ingredients" such as excipients or fillers?

No, IronAid™ is composed solely of milk protein (casein) bonded to ferric iron, and does not contain other excipients.

[3] Explain the entire process through which the finished form of IronAid™ is derived, from the initial source, to intermediate processing, to the finished product.

In the proprietary manufacturing process for IronAid™, milk protein is added to a mixture of succinic anhydride under controlled pH conditions. To this mixture, iron salt (ferric iron) is added, and after sufficient stirring, the iron protein succinylate mixture is dried by spray drying, and is packaged.

[4] Provide the chemical structure for IronAid™.

Please see the attached sheet. That page contains the schematic representation of IronAid™ and is thus proprietary; it should be redacted in its entirety before Chemi's NDI Notification for IronAid™ is placed on the public docket. By separate correspondence, I will send the proposed redacted version of the IronAid™ Notification in order to protect the company's proprietary information and trade secrets.

[5] Provide suggested conditions for use. For example, "Take with food" or "Take on an empty stomach."

There are no special requirements for the use of dietary supplements containing IronAid™, such as the need to take on an empty stomach. In the revised Notification, we have made clear that no suggested conditions for use are required or recommended by Chemi.

[6] Are there any limitations on the duration for use of IronAid™? For example, "Do not take for more than x consecutive days."

No, there are no such limitations on duration; and we will make sure that this is stated expressly in the revised Notification. IronAid™ is a source of iron, and like other iron compounds, is taken long-term, normally for many months and years, for the treatment of iron deficiency.

[7] Is there a target population for IronAid™? For example, iron-deficient children.

No, there is no one, particular target population for IronAid™. Any person, and especially women of child-bearing age and malnourished children may be iron-deficient, and thus would benefit from taking IronAid™.

[8] Are there any populations who should not consume IronAid™? For example, pregnant or lactating women.

No, there are no contraindications for IronAid™, nor any populations for whom IronAid™ in the amounts on the recommended label would be at all unsafe. Also see answer to [7].

Finally, you will find that with this revised NDI Notification, we have attached copies of all of the articles and studies referenced in the text of the Notification and in the footnotes. Per your voice mail message of March 28, 2002, we have included three copies of all materials, that is, one original and two copies of the Notification and all attachments.

Sincerely,

Susan D. Brienza
on behalf of Chemi Nutraceuticals, Inc.

SDB:pah

Enclosure

cc: Mr. Scott Hagerman (via Federal Express)

Submitted to:

Attn: Ms. Gloria Chang
Re: NDI Notification
Food and Drug Administration
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740-3835

IronAid™

Iron Protein Succinylate

New Dietary Ingredient Notification Under 21 C.F.R. Sec. 190.6

Revised and Supplemented, April 5, 2002

Submitted by:

Chemi Nutraceuticals, Inc.

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#137198

IronAid™ Iron Protein Succinylate (IPS)

Introduction and Background on the Ingredient

This New Dietary Ingredient Notification is submitted pursuant to 21 C.F.R. § 190.6 and Section 8 of the Dietary Supplement Health and Education Act. This Notification concerns the new dietary ingredient IronAid™ Iron Protein Succinylate ("IPS" or "IronAid™"). IPS is manufactured by Italfarmaco Spa of Italy, which is represented by its subsidiary Chemi Nutraceuticals, Inc. ("Chemi Nutra") in the U.S.

Chemi Nutra will not sell IPS directly to consumers, as a finished supplement product nor as an ingredient in a finished product, but rather will sell it to manufacturers and marketers of dietary supplements, in bulk, for inclusion as a dietary ingredient in a dietary supplement. IronAid™ is a raw material (ingredient), which will be marketed to the nutritional products industry, for use in dietary supplements. In form, IronAid™ is a reddish-brown colored, free-flowing powder.

IPS, to be used for iron supplementation, is a form of iron that is easy to digest. Iron deficiency anemia is a significant problem among certain high-risk populations. This is exacerbated by the fact that iron supplementation is often poorly tolerated due to gastric upset as well as by the poor absorption of those products designed to minimize gastric intolerance. IPS exhibits pH-dependent solubility designed specifically to overcome gastric tolerance and absorption problems. Specifically, IPS is insoluble at gastric pH, and soluble at intestinal pH, which helps prevent the iron gastric intolerance associated with iron supplementation while maintaining superior absorption.

Pharmacological studies also show that IPS does not bypass the transfer system of the intestinal muscosa that regulates iron uptake by blocking iron

transfer when sufficient iron is already present in the body. This means that IPS is unlikely to achieve iron overload even at very high amounts.[1]

On the basis of the extensive scientific information and data presented below, Chemi has concluded that a dietary supplement containing IPS will reasonably be expected to be safe, the standard required by 21 C.F.R. § 190.6 (a).

History of Safe Use of IPS

IPS has an extensive history of safe use under the trade names Ferplex, Ferrolat, Stratofer, Legofer, Prtoeoferrina, Ferrofolin simplex, Folinemic ferro, Ferremon, Pernexin, Rekor ferro, Ferlatum, Fisiofer, Ferxal, Fetrival, Hemo-Q, Lactoferrina, and Ferrocur, and has been studied under the research designation of ITF 282. ITF 282 is identical to IPS and was studied in the same amounts. Substantial preclinical toxicological data for IPS also exists.

IPS has been sold as a pharmaceutical for 15 years in the following countries: Italy, Spain, Portugal, Greece, Turkey, Pakistan, India, South Korea, Mexico, Colombia, Argentina, Brazil, Chile, Albania, Bosnia, Bulgaria, Czech Republic, Ecuador, Serbia, Macedonia, Hungary, China, Paraguay, Croatia and Venezuela. The daily dosage for the product in all of these countries is 1600 mg (80 mg total elemental iron content). This dosage is usually taken in two equally divided doses of 800 mg each (40 mg total elemental iron content). The number of dosage days consumed to date is approximately 400,000,000.

Italfarmaco has an Adverse Event Reporting ("AER") system for its IPS. The findings of that AER system from January 1, 1995 through December 31, 1999 are summarized in an Italfarmaco internal report titled, Iron Protein Succinylate, Periodic Safety Update Report, issued on February 1, 2000. That internal report covers an estimated 3.5 million doses, with 800 mg (40 mg total iron) per dose.

The Italfarmaco internal report indicates that there were no regulatory actions regarding IPS taken for safety reasons during the five-year period covered by the report. Similarly, no spontaneous adverse events were reported. The Italfarmaco report concludes with the following observations:

- No changes in characteristics or severity of reactions from preclinical data was noted.
- No increase in frequency of reported either listed or unlisted reactions occurred.

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[1] Pagella, P.G., Pharmacological and Toxicological Studies on an Iron Succinyl-Protein Complex (ITF282) for Oral Treatment of Iron Deficiency Anemia, Arnzneimittel-Forschung Drug Research, 34 (II): 952-958, 1984.

- No serious adverse reactions were reported.
- No drug interactions have been noted; further, the lack of H2 antagonist interaction has been shown in a clinical trial.
- Dosage form (liquid versus solid) does not change tolerability.
- No differences in tolerance were noted in dosages from 1600 mg to 2400 mg per day (80 mg to 120 mg total iron).

The report also notes that data is still being collected regarding overdose, abuse and misuse, and long-term consumption effects, since the AER system remains in place.

Recommended Conditions of Use

IronAid™ is designed for use in any dietary supplements that might normally contain iron. Serving sizes are based on total elemental iron, which is five percent of the total weight of the IronAid™ IPS complex. Typically, the product is consumed in two servings. Recommended serving size ranges from 20 mg to 800 mg of IronAid™ IPS (1 to 40 mg of total elemental iron) taken twice per day. Amounts lower than 800 mg could be taken as a single serving or in multiple servings throughout the day as long as the total daily intake does not exceed 1600 mg per day (80 mg total elemental iron).

The safety data contained in this Notification is based on studies at the 800 mg/day level and the 1600 mg/day level. Please note that the recommended conditions of use for this Notification, and which will be recommended to dietary supplement manufacturers who purchase Chemi Nutra's IPS in bulk, is 800 mg/day.

There are no special requirements for the use of dietary supplements containing IronAid™, such as the need to take on an empty stomach. No suggested conditions for use are required or recommended by Chemi. In addition, there are no limitations on duration. IronAid™ is a source of iron, and like other iron compounds, is taken long-term, normally for many months and years, for the treatment of iron deficiency.

There is no one, particular target population for IronAid™. Any person, and especially women of child-bearing age and malnourished children may be iron-deficient, and thus would benefit from taking IronAid™. Finally, there are no contraindications for IronAid™, nor any populations for whom IronAid™ in the amounts on the recommended label would be at all unsafe.

Chemi Nutra will make clear to all purchasers of IPS that if, in their finished product dietary supplement, they use different amounts of IPS or different

recommended conditions of use than those in this Notification, then they must submit their own New Dietary Ingredient Notification to the FDA.

The data suggests that the sole limiting factor on safety is the level of safe iron intake in general – not the safety of IPS specifically. Serving size recommendations for IronAid™ should therefore follow the same recommendations as for any form of supplemental iron, including warning statements on accidental poisoning found in 21 C.F.R. § 101.17. Further, manufacturers must use child resistant closures and packaging where that total iron content per unit exceeds the allowable maximums as required under 21 C.F.R. § 111.50.

All purchasers of Chemi Nutra's IPS will be given a copy of this Notification so that they may follow the recommended conditions of use and label and packaging requirements as set forth in this document.

Preclinical Safety – Animal Studies

There have been numerous toxicology and animal studies of IPS. In his review of IPS safety, [2] Forster concludes, "The available toxicology and safety profile of this product offers ample assurances of the safety of iron protein succinylate in clinical use." He draws this conclusion from the work of several researchers who examined both acute and chronic toxicity in animals. The work was conducted in animals for equivalency with of a dose of 1.5 mg/kg/day total elemental iron in humans.

Acute Toxicity

Biagi in 1985 studied the effects of oral administration of high doses of IPS in rats and mice (5 male and 5 female of both rats and mice) [3]. No reactions to treatment and no mortalities were noted at doses up to 4,000 mg/kg. The LD50 is therefore greater than 4,000 mg/kg. Intraperitoneal injection of IPS yielded an LD50 of 707 mg/kg for both rats and mice. There was no apparent difference between males and females.

Sub-acute Toxicity

A 30-day course of oral administration of IPS in rats at doses of 500, 1,000 and 1,500 mg/kg/day also showed no significant adverse effects.[4] Studies done on

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[2] Forster, R., Iron protein succinylate: preclinical safety assessment, International Journal of Clinical Pharmacology, Therapy and Toxicology, 31:2, 53-60, 1993.
[3] Biagi, GL, Pharmatoxicological Report on Ferrolat (Iron Protein Succinylate), Institute of Pharmacology, University of Bologna, 1985 (unpublished report).
[4] ItalFarmaco, Scientific Profile on Iron Proteinsuccinylate (IPS), p.10, Milan (unpublished report).

beagles for 28 days at 100 and 200 mg/kg/day and for a total of 44 days, divided into two periods of fourteen days at a dose of 400mg/kg/day followed by an increase in dose to 800 mg/kg/day for 30 days, also yielded no significant adverse effects.

Chronic Toxicity

Long-term studies (52 weeks) in both rats and dogs were conducted. The (Wistar) rat study included 50 male and 50 female rats at doses of 0, 11.6, 21.2, 42.5 and 85 mg/kg.[5] Parameters monitored included mortality, body weight, food and water consumption, hematology, blood chemistry, urinalysis and fecal blood, in addition to clinical observation. Necropsy analysis was performed to determine organ weights and morphology and pathological histology. Other than a slight increase in body weight of male animals receiving IPS, there were no findings of toxicological significance.

The beagle study was done on 4 male and 4 female animals at dose levels of 0, 100, 200 and 400 mg/kg/day.[6] In addition to clinical signs, parameters included body weight, food and water consumption, ophthalmology, ECG, hematology, blood chemistry, urinalysis and fecal blood. Necropsy included organ weights and full histopathology. The only significant changes versus control were reduced weight gain in males at 200 and 400 mg/kg/day and slightly increased iron content in the liver and spleen at 400 mg/kg/day. However, histopathological findings on these organs revealed no changes consistent with iron overload damage.

Reproductive Toxicity

The effects of IPS on male and female fertility as well as peri- and postnatal reproductive function and fetal toxicity have been studied in rats. Fetal toxicity has also been studied in rabbits.

Fertility

Fertility of male Sprague-Dawley rats was tested on 4 groups of 6 animals each at doses of 0, 500, 1,000 and 1,500 mg each by oral gavage (Biagi 1985). Treatment began 8 weeks prior to mating with two untreated females for each male. Treatment group males were tested for testes weight and weight gain at the end of the study. Examination of females and fetuses was conducted 20 days following mating. Parameters measured were number of fertilized females, number of fetuses per female, weight of fetuses and proportion of live to dead fetuses. None of theses parameters yielded any adverse effects.

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[5] Fish, LE, ITF 282: One year oral toxicity in rats (pathology report), Huntingdon Research Centre, Cambs., UK (unpublished report) 1986.

[6] Harling, RJ, ITF 282: Oral Toxicity Study in Beagle Dogs, Huntingdon Research Centre, Cambs., UK (unpublished report) 1989.

Fertility of female Sprague-Dawley rats was tested on 4 groups of 12 animals each at doses of 0, 500, 1,000 and 1,500 mg each by oral gavage (Biagi 1985). Treatment began 8 weeks prior to mating and continued until the fourth day following mating with two treated females for each untreated male. Half (6) of the females from each treatment group were sacrificed at day 20 following the beginning of mating, with the remainder allowed to deliver spontaneously. Parameters measured were number of fertilized females, number of fetuses per female, weight of fetuses, proportion of live to dead fetuses and weight of pups at weaning. None of theses parameters yielded any adverse effects.

Peri- and Postnatal Function and Teratogenicity

Four groups of 25 pregnant female Sprague-Dawley rats received IPS by oral gavage at dose levels of 0, 100, 300 and 900 mg/kg.[7] Treatment began on day 15 of gestation and continued until day 21 postpartum. Parameters measured in the dams were body weight change, food consumption or duration of gestation. None of these showed any adverse effects. Measurements of litter number, size and weight also showed no adverse effects. However, measurements of litter mortality and loss yielded some changes. There was a small but statistically significant increase in pup mortality in the first four days postpartum at the highest dose level of 900 mg/kg. Countering this result in terms of overall survivability was an accompanying reduction in total litter loss as the dose increased.

Effect Of IPS On Peri- And Postnatal Development In The Rat

Parameter	Group 1 Control	Group 2 100 mg/kg/day	Group 3 300 mg/kg/day	Group 4 900 mg/kg/day
No. of females mated	25	25	25	25
Total litter loss	3	2	1	0
No. of litters	17	18	20	19
Mean duration of gestation	21.9 day	22.0 day	21.9 day	21.7 day
No. of live pups/litter (day 0)	11.1	10.0	11.0	10.2
No. of pups/litter (day 4)	11.1	9.8	10.8	9.1
No. Of pups/litter (day 21)	11.0	9.7	10.7	9.1
Litter weight (day 0)	69.3 g	61.1 g	67.0 g	61.7 g
Litter weight (day 21)	462 g	442 g	453 g	403 g
Sex ratio M:F (day 21)	0.77	1.19	1.14	0.98

[7] Mayfield R, Kamara J, Gibson WA, Effect of ITF 282 on periand post-natal development of the rat, Huntingdon Research Centre, Cambs., UK (Unpublished Report) 1985.

Age showing surface righting	2.6 day	2.4 day	2.5 day	2.8 day
Age showing air righting	15.3 day	15.2 day	15.3 day	15.1 day

Including lost litters, 20 total control group pregnancies resulted in 187 surviving offspring at day 21. Sixty total IPS-treated group pregnancies resulted in 561 surviving offspring at day 21. In both cases, the ratio of survivors to pregnancies is 9.35. Therefore, IPS treatment did not result in any adverse effect on the overall survival of the offspring.

Growth and development of the offspring was also measured through observation of attainment of reflexes. No adverse effects were noted.

Fetal Toxicity

Four groups of 25 pregnant female Sprague-Dawley rats were given respectively 0, 100, 300 and 900 mg daily of IPS.[8] Treatment began on day 6 of gestation and continued through day 15. On day 20 the animals were sacrificed and fetuses were examined. The pregnant females showed no adverse effects. Litters were measured for pre-and post implantation loss, weight, size, sex ratios and visceral and skeletal abnormalities. No adverse effects were found.

Four groups of 16 pregnant female New Zealand rabbits were given respectively 0, 100, 300 and 900 mg daily of IPS.[9] Treatment began on day 6 of gestation and continued through day 18. On day 29 the animals were sacrificed and fetuses were examined. The pregnant females showed no adverse effects other than a slight reduction in weight gain during the mid and late stages of treatment at the highest dosage level, accompanied by a significant depression of food intake. Litters were measured for pre-and post implantation loss, weight, size, sex ratios and visceral and skeletal abnormalities. No adverse effects were found.

Genetic Toxicity

Iron protein succinylate has been studied in a series of mutagenicity assays. Tests were included for each of the three principal indicators of chemically induced genetic damage, namely the induction of DNA repair (Biagi 1985), point

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[8] Mayfield R, John DM, Effect of ITF 282 on pregnancy of the rat, Huntingdon Research Centre, Cambs., UK (Unpublished Report) 1985.

[9] Mayfield R, Kamara J, Masters R, Effect of ITF 282 on pregnancy of the New Zealand white rabbit, Huntingdon Research Centre, Cambs., UK (Unpublished Report) 1985.

mutations[10] and chromosomal breakage[11]. Tests were conducted using both in vitro and in vivo assay methods. There was no evidence of mutagenic activity after treatment with iron protein succinylate in any of the studies performed.

Clinical Safety

At least 16 clinical trials and 1 post-marketing surveillance study have been conducted on IronAid™ IPS. In the 16 clinical trials (14 controlled and 2 uncontrolled) a total number of 352 patients suffering from iron deficiency (11%) and iron deficiency with anemia (89%), were treated with IPS at the dosage of 80 mg trivalent iron daily for 30 to 60 days. Similarly, 80 mg of elemental iron per day is the maximum recommended use of IPS in this Notification.

In pediatric studies included among these 16 trials, the daily dosage of IPS was adjusted according to the weight of the patients (20 mg bid if under 15 kg, and 40 mg if above 15 kg). The inclusion criteria for most of the trials were: Hb less than 11 g/ 100 ml, serum iron concentration less than 40/50 mg/ml, and transferrin saturation rate less than 15%.

In the controlled trials the comparison of the efficacy and tolerability of IPS was performed against ferritin (8 studies, 130 + 126 patients, respectively), iron gluconate (3 studies, 50+ 50 patients, respectively), iron sulphate (2 studies, 30 + 30 patients respectively), and iron polistyren sulphonate (1 study, 17 + 19 patients, respectively). IPS performed as well or better than any of the other four iron compounds tested, with respect to both efficacy and tolerability, in all of these studies. No serious adverse events were reported.

The post-marketing surveillance study was performed with nearly 3000 patients (n=2996) with iron deficiency due to obstetric or gynecologic etiology and treated with IPS at the usual dosage of 80 mg iron/day for periods ranging from 30 to 120 days.

The results are summarized in the following tables:

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[10] Monaco M, Ferrolat: Ames test, Test for forward mutation in S. pombe P1 and test for mitotic gene conversion in S. cerevisiae D4. Life Science Research Roma Toxicology Centre, Pomezia (Unpublished Report) 1983.

[11] Mosesso P, Evaluation of the clastogenic action of Ferrolat on mouse bone marrow erythrocytes in vivo in the micronucleus, Life Science Research Roma Toxicology Centre, Pomezia (Unpublished Report) 1983.

Type Of Patients

Type of Patient with Iron Deficiency Anemia	Patients admitted	Patients evaluated for efficacy	Patients evaluated for tolerability
Pediatrics	49	41	49
Adults	168	146	168
Obstetrics	135	130	90
TOTAL	**352**	317	307
Obst. & Gynecology (Post Marketing Surveillance)	2996	2993	2996
OVERALL TOTAL	**3348**	**3310**	**3303**

The following table shows that less than 7.6% of all of the 3,303 patients evalated for tolerability of IPS had any adverse reactions to IPS at all. Of the 7.59 % who did, these adverse reactions were minor, not serious.

Adverse Reactions By Type

Type of Adverse Reaction	Number of Patients	% of treated patients (n=3303)	% of all Adverse Reactions
Diarrhea	65	1.9	25.2
Nausea	44	1.3	17.1
Gastric pain	61	1.8	23.7
Heartburn	46	1.3	17.8
Vomiting	13	0.39	5.0
Constipation	7	0.21	2.7
Gastric discomfort	2	0.06	0.7
Intestinal discomfort	4	0.12	1.5
Other symptoms	17	0.51	6.6
TOTAL	**257**	**7.59**	**100**

Summary on the Safety of IPS

Under 21 C.F.R. § 190.6 (a), the standard for a new dietary ingredient premarket Notification is that the manufacturer present the basis on which it has concluded that "a dietary supplement containing such dietary ingredient will reasonably be expected to be safe." In this Notification, we have documented the safety of IPS, at the amount of 80 mg of elemental iron per day, in three ways: animal studies, human clinical trials, and a history of safe use in other countries for 15 years. Copies of all articles and reports cited herein are attached, pursuant to 21 C.F.R. § 190.6 (b)(4). Together, these articles and reports, in conjunction with the analysis and charts above, demonstrate that a dietary supplement containing IPS at the level of 80 mg of elemental iron per day, and under the conditions of use above, will reasonably be expected to be safe.

CHEMI NUTRACEUTICALS, INC.

By: _____
Scott Hagerman, President

Date: April 8, 2002